Remarks

The examiner's withdrawal of the rejection of claims 16 and 23 under 35 U.S.C. §102(b) claims 16-23 under 35 U.S.C. §103(a) is appreciated.

Rejection Under 35 U.S.C. §112, first paragraph-written description

Claims 16-23 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Legal Standard

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). All that is required is that the specification provides sufficient description to **reasonably** convey to those skilled in the art that, as of the filing date sought, that the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would

recognize that the inventor had possession of the claimed invention. M.P.E.P. § 2163(I), citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 66, 48 USPQ2d 1641, 1646 (1998).

In a recent decision by the Board of Patent Appeals and Interferences, the Board warned that it is an improper analysis to determine that the claims are directed to an invention which is broader than that which is described in the specification since the written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. Thus the Board re-emphasized that the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *LizardTech Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-34, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

Analysis

Applicants are addressing the problem of how to produce recombinant organisms that can produce *high levels of medium chain length polyhydroxyalkanoates* (*see* page 3, line 27 to page 4, line 3 and page 8, lines 27-30) while avoiding increasing the level of 3-hydroxyacid in the feed, avoiding the use of 3-propionic acid in the feed, and avoiding the generation of free propionic acid in the cytosol. The solution, as described on page 4, lines 5-15, page 8, line 27 to page 9, line 12, and defined by the claims, is to provide, in addition to the other enzymes for polyhydroxyalkanoate production (beta-ketothiolase, acetyl CoA reductase and PHA synthase, all of which are known), a CoA aldehyde dehydrogenase which directly converts any aldehydes generated from the alcohols used as co-feed, into the corresponding acyl-CoA.

The claims define a recombinant organism selected from the group consisting of bacteria, yeast, fungi and plants for producing polyhydroxyalkanoates, comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase. As discussed in the below, CoA-dependent aldehyde dehydrogenase, PHA synthase, Acyl CoA synthetase and Acyl CoA transferase are all known in the art. Recombinant production of PHA is also known in the art.

The specification from page 9, line 13, to page 10, line 8, describes sources for CoA-dehydrogenase (also see page 10, lines 27-30). Genes involved in PHA synthesis as well as their sources are known in the art as disclosed on page 3, lines 9-12 of the specification (see also, Madison and Huisman, *Microbiol. Mol. Bio. Rev.* 63(1):21-53 (1999) ("Madison", a copy of which was attached with the response filed on September 8, 2006)), and U.S. Patent 5,250,430 to Peoples, et al. Methods for identifying genes via complementation, including genes encoding PHA synthases are well-known to those skilled in the art (*see e.g.*, Nishikawa, et al., *Curr. Microbiol.* 44(2):132-135 (2002); a copy of which was attached with the response filed on September 8, 2006)).

Acyl CoA synthetase activity is referenced in Figure 1 of the specification. Genes encoding acyl CoA synthetase activity are well-known to those skilled in the art. *See e.g.*, Black, et al., *J. Biol. Chem.* 267:25513-25520 (1992); van Beilen, et al., *Molecular Microbiology* 6:3121-3136 (1992); and Matesanz, et al., *J. Mol. Biol.* 291:59-70 (1999) (copies of which were attached with the response filed on September 8, 2006).

Acyl CoA transferase activity is depicted in Figure 1. Genes encoding acyl CoA transferase activity are well known to those skilled in the art. *See e.g.*, Madison, and Sohling, et

al., *J. Bacteriol.* 178:871-880 (1996) (a copy of which was attached with the response filed on September 8, 2006).

The Examiner alleges the claims are drawn to microorganisms comprising enzymes whose structure is not disclosed. Applicants respectfully draw the Examiner's attention to the MPEP§2163-"As explained by the Federal Circuit.... 3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084. ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.)". Similarly here the claims define recombinant organism containing genes which have already been described in the art. As affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art". As already discussed, the genes necessary to make the claimed organisms were already described in the art. According to the Examiner, Applicants

are required to disclose adequate structural feature of the genus (genes) used to make the organism, such that one of ordinary skill in the art can easily practice the claimed invention. The Examiner also alleges that "the genus of any CoA-dependent aldehyde dehydrogenase and any PHA synthase is a very large genus" and that these genes have different structures. Applicants respectfully point out that not only are the individual genes and their structures already known in the art, Applicants have provided the sources of these genes, and providing Genbank accession numbers (see the specification at least from page 2, line 13 until page 10, line 12 and page 9, line13, until page 10, line 8.

According to the MPEP §2163, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406".

The question is whether the genes are adequately described in such a manner that a skilled artisan would recognize that applicants were in possession of the claimed invention. Applicants have extensively demonstrated that these genes have been described in the art. The claims do not define genes. The claims define organisms which are genetically engineered to express genes, each of which has already been described in the art; however they are expressed in a combination that leads to the avoidance of accumulation of 3-hydroxyacid in the cytosol of PHA producing organisms. Methods to heterologously expressing said genes are well known in

the art. Clearly, the requisite genes as well as their structures are well known in the art, and these genes have been individually successfully incorporated in organisms that do not originally express them. It is established that they can each be heterologously expressed (knowledge in the art), and the specification in the Examples describes heterologous expression of the genes in the novel combination recited in the claims (i.e CoA-dependent aldehyde dehydrogenase and a PHA synthases genes).

A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In rejecting a claim, the examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. The Examiner has not done so.

It is clear from the description in the specification and from the information in the art that claims 16-23 satisfy the written description requirement.

Rejection Under 35 U.S.C. §112, first paragraph-enablement

Claims 16-23 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Applicants respectfully traverse this rejection.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under §112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art

without undue experimentation. *See, e.g., Amgen v. Hoechst Marion Roussell*, 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d 1361, 1365, 42 USPQ2d1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). *See also In re Fisher*, 427 F.2d, 833, 839, 166 USPQ 18, 24 (CCPA 1970); *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966, 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *citing Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the

breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). **There is no requirement for examples**. The Supreme Court also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling *In re Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts."). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. MPEP § 2164.01(b).

In *In re Douglas v. United States* 510 F.2d 364, 184 U.S.P.Q. 613 (Ct. Cl.1975) the Court of Claims noted that a patentee cannot "be expected to foresee every technological problem that may be encountered in adapting his idea to a particular use. Some experimentation and exercise of judgment is to be expected." Further, the Federal Circuit noted in *In re Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, citing *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916), wherein the court emphasized that some inventions cannot be practiced without adjustments being made to adapt them to the particular context. In such a situation, a specification is sufficient if it gives adequate guidance to one skilled in the art on how such adjustments are to be made.

Analysis

To comply with the enablement requirement, the specification must teach a skilled artisan how to make and use the claimed invention. The claims define a recombinant organism for producing polyhydroxyalkanoate, selected from the group consisting of bacteria, yeast, fungi and plants, comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase. The organism further comprises a gene encoding acyl-CoA tranferase, acyl-CoA synthetase, β-ketothiolase, and acetacetyl Co-A reductase.

As previously discussed, Applicants are addressing the problem of how to provide recombinant organisms that can produce *high levels of medium chain length polyhydroxyalkanoates* (*see* page 3, line 27 to page 4, line 3 and page 8, lines 27-30) while avoiding increasing the level of 3-hydroxyacid in the feed, avoiding the use of 3-propionic acid in the feed, and avoiding the generation of free propionic acid in the cytosol.

The genes needed to produce the claimed organisms are not only known in the art. They have been heterologously expressed individually. A skilled artisan therefore knows how to clone the requisite genes into a system that does not naturally express the gene to effect expression of the enzyme activity.

Sources for CoA-dehydrogenase are known in the art and are disclosed in the specification from page 9, line 13, until page 10, line 8 (*see* also, page 10, lines 27-30). Genes and techniques for developing recombinant PHA producers are known in the art (*see* Madison). A skilled artisan, from the information in the art, would know which choices of the disclosed genes would be successful. For example, U.S. Patent No. 5,534,432 to People's et al (People's) discloses methods used to isolate genes encoding beta-ketothiolase, acetoacyl-CoA reductase,

PHB polymerase and PHA polymerase (from *Z. ramigera, A. eutrophus, N. salmonicolor and P. oleovorans*), their expression products as well as the sequences regulating their expression. Peoples also discloses how to express these genes in plants. Poirier, et al., Appl. Environ. Microbial. 67(11):5254-60 (2001) ("Poirier", a copy of which is attached) discloses the expression of PHA biosynthesis genes in yeast and discusses their successful expression in plants, leading to the production of PHAs in these systems. The art is very well developed in the process of expressing the genes recited in the claims (albeit not in the same combination), in the heterologous systems recited in claim 1, with numerous papers published to this effect, and patents issued (See for example Poeples and U.S. Patent No. 6,329,183 to Skraly, et al.). A point of novelty here is that Applicants have provided organisms that can produce high levels of medium chain length polyhydroxyalkanoates while avoiding increasing the level of 3-hydroxyacid, by providing the organisms with the ability to also express in combination with the PHA biosynthesis genes, a CoA-dependent aldehyde dehydrogenase, to scavenge 3-hydoxyacids. There is sufficient guidance in the specification to construct plasmids and express the claimed genes (*see* Examples in the pending application). In addition, the experimental protocols are routine and expression vectors, restriction enzymes and ligation enzymes are commercially available. Although there is no need for examples, Applicants **have provided examples** to show that one can isolate, identify and express the enzymes in organisms as recited in the claims.

The Examiner alleges that Applicants have not provided a method of making all of the variant mutants of the *E. coli* CoA-dependent aldehyde dehydrogenase and PHA synthase, and have not shown that any of the variants and mutants or recombinants of these enzymes would successfully work. Applicants respectfully point out that patents are not required to disclose every species encompassed by the claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d

488. (Fed. Cir. 1991). As set forth in *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "the enablement requirement is met if the description enables any mode of making and using the invention." Secondly the claims are not drawn to genes. The claims define a recombinant organism for producing polyhydroxyalkanoate comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase. The test for enablement should be whether a skilled artisan, with the guidance in the specification, can make and use the claimed recombinant organism. The individual genes that are required to produce the organisms as extensively discussed are not novel. They have been known in the art for twenty years and used for heterologous expression (see the specification at least from page 2, line 21, until page 3, line 12 for a discussion of the heterologous expression of PHA synthase genes, Poirier and Toth, et al., *Appl. Environ. Microbiol*, 65(11):4973-80 (1999) cited by the Examiner in the office action dated May 11, 2006, or Madison)), although not in the combination recited in the claims, which is beneficial in preventing accumulation of 3-hydroxy acid in the cytosol of the PHA producing organism. It is unclear how using genes that are known, with known methods of heterologous expression to make the claimed organisms cannot be enabled. Furthermore, any mutants and variants of these genes that do not work are outside the scope of these claims, since the claims require that the organism be able to produce PHA. Not only are all the genes to be incorporated into the recombinant organism claimed by the Applicants well known in the art, Applicants have provided numerous working examples of recombinant *E. coli* producing PHA as claimed. It is very clear from the disclosure in the specification and the state the art, that a skilled artisan would be able to make recombinant bacteria, yeast, fungi and plants that express all the genes that are recited in the claims, for the production of PHAs.

It is well established that a specification is presumed to be enabling. A *prima facie* case of non-enablement can only be made upon a showing of evidence, ***not argument,*** of why one skilled in the art would not be able to make and use the claimed subject matter. Even assuming *arguendo* that the examiner has done so, Applicants have rebutted this with reference to support not only in the specification but in the literature. Therefore, claims 16-23 are enabled.

Allowance of claims 16-23 and rejoinder and allowance of claims 1-12 and 24-35 is respectfully solicited. Should the claims not be in condition for allowance, the undersigned requests an interview with the Examiner and his supervisor.

Respectfully submitted,

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Date: March 29, 2007

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